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Paper

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Carol A. Spiegel)

ALICE M. **WANG**, MICHAEL E. DOYLE
and DAVID F. MARK

Junior Party,
U.S. Patent 5,219,727
U.S. Patent 5,476,774

v.

GEORGE **MURAKAWA**, R. BRUCE WALLACE,
JOHN A. ZAIA and JOHN J. ROSSI

Senior Party,
Application 07/402,450

Patent Interference No. 105,055

Before: SCHAFFER, TORCZON and SPIEGEL, Administrative Patent Judges.

SPIEGEL, Administrative Patent Judge.

DECISION ON PRELIMINARY MOTION
(Murakawa preliminary motion 1)

For reasons set forth in the MEMORANDUM OPINION and ORDER (Paper 36) of November 5, 2003, the Board concluded that all of the involved Murakawa claims, i.e., Murakawa claims 34-35, 38-39 and 42-47 are barred under 35 U.S.C. § 135(b)(1) by the 1993 Wang U.S. Patent 5,219,727. Murakawa was ordered to submit one (1) claim that interferes with the claimed subject matter of Wang patents 5,219,727 and 5,476,774 and is not time barred by § 135(b)(1) in order for this interference to continue (Paper 37).

Before us for consideration is Murakawa preliminary motion 1 to add proposed Murakawa claim 50 and to designate it as corresponding to Count 1. We deny Murakawa's motion because its proposed claim 50 does not interfere with the subject matter of the involved Wang claims.

I. Introduction

This interference concerns a polymerase chain reaction ("PCR") - based method for determining the amount of a target nucleic acid sequence in a sample by simultaneously amplifying the target nucleic acid sequence in a sample and a known amount of an added internal standard sequence ("control sequence"¹) with the same primer pair in a single reaction mixture (Count 1). (See Paper 36, pp. 2-3 for a more complete description of the interfering subject matter.)

Briefly, PCR is an enzymatic DNA amplification method involving repeated cycles of defined steps. The required reagents include a DNA polymerase enzyme, each of

¹ In this decision, the terms "standard," "reference" and "control" are equivalent when used in reference to the added internal standard nucleic acid. Furthermore, in this decision, the term "predetermined quantity" is equivalent to the term "predetermined amount."

the four nucleotide building blocks of DNA (i.e., dNTPs A, T, G and C), a source of template DNA containing a target sequence and two oligonucleotide "primers" designed to be complementary to the bases at the 3' ends of the target DNA sequence.

Amplification takes place in three stages, i.e., denaturation, annealing and extension. Denaturation of template DNA separates the double-stranded DNA into two single strands. The primers bind, i.e., hybridize, to their complementary DNA sequences on the single strands during annealing (a large excess of primers is used to ensure that the single strands will bind to the primers instead of each other), resulting in a nucleic acid molecule that is partially double-stranded where the primer is hybridized and partially single stranded where the primer has not hybridized. The polymerase uses the annealed primer as a substrate and sequentially adds a nucleotide to the 3' end of the primer which is complementary to the nucleotide which is "across" from it on the single-stranded portion of the molecule to produce a "primer extension product." Each time this three-step cycle is repeated the products of the previous cycle become new templates for the next cycle such that in each new cycle the amount of the target DNA essentially doubles.

In reverse-transcription PCR, mRNA is transcribed back into cDNA which is then used as the template for PCR.

[See generally, U.S. Patent 4,683,195 issued July 28, 1987 to Mullis et al. (Mullis), entitled "Process for Amplifying, Detecting, and/or Cloning Nucleic Acid Sequences" (Ex 1013); Paper 36, p. 2, n.1.]

According to Wang,

[b]ecause [PCR] amplification is an exponential process, small differences in any of the variables which control the reaction rate, including the length and nucleotide sequence of the primer pairs, can lead to dramatic differences in the yield of PCR product. Analyses which use two sets of unrelated primers, therefore, can only provide a relative comparison of two independent amplification reactions rather than an absolute measure of the mRNA concentration. [Exs 2002 and 2003 at c. 1, ll. 57-65.]

Further according to Wang,

...differences in primer efficiency are difficult parameters to regulate for quantitative analysis. ... As indicated in FIG. 4, the efficiency of amplification by these different primer sets under the same PCR amplification conditions varied over a range of several orders of magnitude. For instance, the IL-1 β primers are 10⁵-fold more efficient than the apo-E primers. Thus, it is critical to use the same primers for amplification of both the target mRNA and the internal standard in any attempts to quantitate mRNA expression by PCR. [Exs 2002 and 2003 at c. 16, l. 62 - c. 17, l. 8.]

Here, Wang '727 claim 1 is not anticipated by proposed Murakawa claim 50 because proposed claim 50 does not explicitly or inherently require use of the same primer pair to amplify both target and reference nucleic acid sequences as required by Wang '727 claim 1. Further, Wang '727 claim 1 is not rendered obvious by proposed Murakawa claim 50 in view of certain prior art because modifying proposed claim 50 as suggested would not have resulted in Wang's claimed invention.

II. Findings of fact (FF)

The following findings of fact are supported by a preponderance of the evidence.

1. The junior party is ALICE M. WANG, MICHAEL D. DOYLE and DAVID F. MARK (Wang).
2. Wang is involved in the interference on the basis of two patents:
 - (i) U.S. Patent 5,219,727 ("the Wang 1993 patent"), which issued June 15,

1993, based on application 07/413,623, filed September 28, 1989, and

- (ii) U.S. Patent 5,476,774 ("the Wang 1995 patent"), which issued December 19, 1995, based on application 08/028,464, filed March 9, 1993.

3. The Wang 1993 patent has been accorded benefit for the purpose of priority of U.S. application 07/396,986, filed August 21, 1989. The Wang 1995 patent has been accorded benefit for the purpose of priority of both U.S. application 07/413,623 (now the Wang 1993 patent) and U.S. application 07/396,986.

4. Both the 1993 and 1995 Wang patents are assigned to Roche Molecular Systems, Inc.

5. The senior party is GEORGE J. MURAKAWA, R. BRUCE WALLACE, JOHN A. ZAIA and JOHN J. ROSSI (**Murakawa**).

6. Murakawa is involved in the interference on the basis of application 07/402,450 ("Murakawa '450"), filed September 1, 1989.

7. Murakawa '450 has been accorded benefit for the purpose of priority of

- (i) U.S. application 07/148,959, filed January 27, 1988 ("Zaia '959"), and
- (ii) U.S. application 07/143,045, filed January 12, 1988 ("Murakawa '045").

8. Murakawa '450 is assigned to the City of Hope.

9. There are two counts in the interference. Count 1 is defined by Wang (5,219,727) claim 1 or any of Wang (5,476,774) claims 5, 15 or 17 or any of Murakawa (07/402,450) claims 34, 35, 44, 46 or 47. Count 2 is defined by Wang (5,476,774) claim 1 or Murakawa (07/402,450) claim 45. [Paper 1, p. 5.]

10. The claims of the parties are:

Wang (5,219,727)	1-10
Wang (5,476,774)	1-18
Murakawa (07/402,450)	34-35, 38-39, 42-47

11. The claims of the parties which correspond to Count 1 are:

Wang (5,219,727)	1-4, 6-10
Wang (5,476,774)	5-7, 10-12, 15-18
Murakawa (07/402,450)	34-35, 38-39, 42-44, 46-47

12. The claims of the parties which correspond to Count 2 are:

Wang (5,219,727)	none
Wang (5,476,774)	1-3, 8-9
Murakawa (07/402,450)	45

13. The claims of the parties which do not correspond to either Count 1 or Count 2, and therefore are not involved in the interference, are:

Wang (5,219,727)	5
Wang (5,476,774)	4, 13-14
Murakawa (07/402,450)	none

14. Murakawa claims 34-35, 38-39 and 42-47 are barred under 35 U.S.C.

§ 135(b)(1) by the 1993 Wang patent 5,219,727 (Paper 36).

15. Murakawa was ordered to submit one (1) claim that interferes with the claimed subject matter of the 1993 and 1995 Wang patents (Wang '727 and Wang '774) and (2) is not time barred by § 135(b)(1) in order for this interference to continue (Paper 37).

Other findings of fact follow below.

II. Murakawa preliminary motion 1

Pursuant to the Order dated November 5, 2003 (Paper 37) and further pursuant to 37 CFR §§ 1.633(c)(2) and 1.627(c)(2), Murakawa moves to add proposed claim 50 to the involved Murakawa '450 application and to designate this claim as corresponding

to Count 1 (Paper 38). Wang opposes (Paper 44); Murakawa replies (Paper 45).

A. There is no interference-in-fact between the subject matter of proposed Murakawa '450 claim 50 and the subject matter of Wang '727 patent claim 1

In order for there to be an interference-in-fact between claims, two way anticipation or obviousness must be established. An interference-in-fact exists when at least one claim of a party that is designated to correspond to a count and at least one claim of an opponent that is designated to correspond to the count define the same patentable subject matter. 37 CFR § 1.601(j). Invention A is the same patentable invention as an invention B when invention A is the same as (35 U.S.C. 102) or is obvious (35 U.S.C. 103) in view of invention B assuming invention B is prior art with respect to invention A. 37 CFR § 1.601(n). A patentable distinction in either direction requires a finding of no interference-in-fact. See Winter v. Fujita, 53 USPQ2d 1234 (BPAI 1999); Eli Lilly & Co. v. Board of Regents of the University of Washington, 334 F.3d 1264, 67 USPQ2d 1161 (Fed. Cir. 2003).

1. comparison of proposed Murakawa claim 50 and Wang '727 claim 1

16. The following chart compares the language of Wang '727 claim 1 and Murakawa proposed claim 50 (emphasis added).

Proposed Murakawa claim 50		Wang '727 claim 1	
50. A process for quantitation of		1. A method for quantifying	
a target viral RNA sequence		a target nucleic acid segment	
in a peripheral blood cell sample which comprises		in a sample, which method comprises the steps of:	
	(i) selecting said target viral RNA sequence;		(a) adding to said sample
	(ii) simultaneously subjecting		
	(a) said sample and		
	(b) a predetermined quantity of at least one synthetic RNA sequence which does not include said target sequence or which includes substantially more nucleotides than said target sequence		a predetermined initial amount of standard nucleic acid segment wherein said standard nucleic acid segment binds to same primers as are bound by said target nucleic acid segment in a reaction mixture;
	to polymerase chain reaction amplification under conditions to simultaneously amplify said target sequence if present in said sample and said reference sequence;		(b) treating said sample under conditions suitable for carrying out a polymerase chain reaction, wherein said nucleic acids are rendered single-stranded and exposed to an agent for polymerization, deoxynucleoside 5' triphosphates, and a pair of oligonucleotide primers, wherein said pair of primers is specific for both the target and standard nucleic acid segments, such that an extension product of each primer of said pair can be synthesized using separate strands of the target and standard segments as a template for synthesis, such that the extension product of one primer, when it is separated from the template strand, can serve as a template for the synthesis of the extension product of the other primer of said pair wherein said amplified target and standard segments are distinguishable by size or by the use of internal probes, wherein said internal probes may be differentially labeled for each of said amplified target and standard segments;
(iii) denaturing the amplification products produced by step (ii);		(c) separating the primer extension product from the templates on which they were synthesized to form single-stranded molecules; (d) repeating steps (b) and (c) on the single stranded molecules produced in step (c) at least once, whereby each repeat of steps (b) and (c) is one amplification cycle;	

	<p>(iv) subjecting said denatured amplification products of step (iii) to hybridization conditions separately and sequentially with labeled probes homologous to said target sequence and to said reference sequence and detecting the presence or absence of the target sequence and the presence of the reference sequence in the amplification products of step (iii) by Southern blot hybridization with said labeled probes,</p> <p>each of said probes being removed from a sequence with which it is hybridized prior to the separate and sequential subsection of said amplification products to hybridization with another of said probes;</p>	
	<p>(v) determining whether said amplified target and reference sequences hybridized with said probes homologous therewith; and</p> <p>(vi) determining the relative quantification of the target sequence by comparison with the amount of signal obtained from the hybridized target sequence with the amount of signal obtained from the hybridized predetermined quantity of the reference sequence.</p>	<p>(e) measuring the amounts of the amplified target and standard segments produced in step (d); and</p> <p>(f) calculating from the amplified target and standard segments produced in step (d) the amount of said target nucleic acid segment present in the sample before amplification.</p>

17. At the outset, it is noted that proposed Murakawa claim 50 and Wang '727 claim 1 present a mix of genus and species elements. Wang '727 claim 1 is generic as to the type of target nucleic acid sequence and sample, whereas proposed Murakawa claim 50 is specific to a viral RNA target sequence and a peripheral blood sample. The reference sequence of proposed Murakawa claim 50 is a synthetic RNA sequence selected from one of two genera, i.e., a reference sequence which does not include the target sequence or a reference sequence which includes substantially more nucleotides than the target sequence. The reference sequence of Wang '727 claim 1 is a species,

i.e., a nucleic acid sequence which is expressly required to bind to the same PCR primers as the target sequence. Both proposed Murakawa claim 50 and Wang '727 claim 1 expressly encompass reference sequences which are distinguishable by size from the target sequence, but only Wang' 727 claim 1 requires the reference sequence to bind to the same primer pair as the target sequence. In addition, proposed Murakawa claim 50 detects the presence or absence of PCR amplification products by a specific method, i.e., by a Southern blot hybridization assay, whereas Wang '727 claim 1 is not so limited. Finally, proposed Murakawa claim 50 determines the relative quantity of target sequence present in the sample before amplification by comparing the amount of signal obtained from the target and reference sequences. Wang '727 claim 1, on the other hand, calculates the actual amount of target sequence present in the sample before amplification.

18. According to Wang,

[t]he amount of the target nucleic acid segment present in the sample prior to amplification is determined using a standard curve. The standard curve is generated by plotting the amount of the standard segment produced in a polymerase chain reaction against varying, but known, amounts of the RNA present before amplification. For accuracy, the amount of standard segment present before amplification is varied by serial dilution of the co-amplification reaction mix. The amount of target segment produced in the polymerase chain reaction is then compared to the standard curve to determine the amount of target segment present in the sample prior to amplification. Alternatively, the standard curve may be generated by plotting the amount of standard and target segments produced against the number of amplification cycles. To ensure accuracy, it is preferred that the number of amplification cycles is varied by removing aliquots from one co-amplification reaction mixture after different numbers of amplification cycles have been completed. [Exs 2002 and 2003 at c. 4, ll. 14-33.]

19. Wang's invention is said to be

...far superior to determinations of the amount of a nucleic acid segment in a sample as a relative, rather than absolute, amount. Further, the method is [said to be] far more accurate than when an absolute amount is derived by employing a second set of oligonucleotide primers to amplify the standard, wherein that set of primers is different from the set used to amplify the target segment. [Exs 2002 and 2003 at c. 4, ll. 34-41.]

20. Murakawa '450 Example I describes amplifying an HIV-1 target sequence with primer pair HIVA and HIVB with subsequent Southern blot detection of primer extension products by hybridization to a radiolabelled probe HIVC (Ex 2006, pp. 8-9). Example VI is said to be "Example I ... repeated with the exception that primer pair actin A and beta actin B is included in the reaction mixture" (*id.*, p. 12). Example VII is said to be "Example I ... repeated with the exception that the maxigene [i.e., reference sequence] primer is included in the reaction mixture" (*id.*).

Both generic reference sequence examples, i.e., a reference sequence which does not include the target sequence or a reference sequence which includes substantially more nucleotides than the target sequence (a "maxigene"), in Murakawa '450 are amplified using a different pair than that used to amplify the target sequence.

21. According to Murakawa '450, its reference sequence provides an

... aid to quantitation. Because the quantity of "maxigene" [or] minigene RNA originally included in the amplification mixture is known, the amount of signal obtained from the maxi or minigene amplification product can be related to the signal obtained from the patient sample. Hence, the relative quantitation of the original amount of authentic HIV-1 in the patient sample is provided. [Ex 2006, p. 7, ll. 1-8.]

Thus, we understand proposed Murakawa claim 50 to determine the "relative" amount target sequence in the original sample by taking an aliquot of the PCR amplification mixture at some point, performing a Southern blot analysis using labelled

probes to detect the presence or absence of the target sequence and the presence of the reference sequence, and comparing the signal obtained from labels hybridized (i.e., bound) to target and reference primer extension products to determine the "relative" amount of target sequence. To wit, the aliquot is applied to a gel and then electrophoresed to separate target and reference primer extension products by size; the separated products are transferred to a membrane; and, labelled probes are separately and sequentially reacted with the transferred products. Presence of the reference sequence is indicated by a signal produced by the label of the probe hybridized to the transferred reference primer extension product. Presence of the target sequence is indicated by a signal produced by the label of the probe hybridized to any transferred target primer extension product. Absence of target signal may indicate no, or an undetectable amount, of target sequence in the original sample in cases where a reference signal is detected; or, may indicate a false negative result in cases where no reference signal is detected. The relative amount of target sequence in the original sample is determined by comparing the amount of signal obtained from the label hybridized to target primer extension product vis-a-vis the amount of signal obtained from the label hybridized to reference primer extension product, i.e., a determination based on a ratio -- a de facto "single point standard curve" -- in contrast to the multi-point standard curve inherent in Wang '727 claim 1. It is uncertain whether the target and reference amplification reactions of proposed Murakawa claim 50 are proceeding equally, e.g., both proceeding with the same efficiency at the same rate. In other words, the method of proposed Murakawa claim 50 is semi-quantitative at best,

whereas the method of Wang '727 claim 1 is quantitative.

2. step (iv) of proposed Murakawa claim 50 is anticipated by Wang '727 claim 1

A single prior art reference anticipates a patent claim if it expressly or inherently describes each and every limitation set forth in the patent claim. Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Inherent anticipation requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citing Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991)). However, "the disclosure of a chemical genus . . . constitute[s] a description of a specific compound" within the meaning of section 102(b) where the specific compound falls within the ambit of a "very limited number of compounds." In re Schaumann, 572 F.2d 312, 315, 316, 197 USPQ 5, 8 (CCPA 1978).

Wang contends that proposed Murakawa claim 50 is not anticipated by Wang '727 claim 1 because Wang '727 claim 1 does not contain step (iv) of proposed claim 50 (Paper 44, pp. 16-17). Wang further contends that such a step is neither recited, taught nor "inherently described" in any other involved Wang claim or patent (id., p. 17).

Murakawa responds that Wang '727 claim 1 contains a generic recitation of proposed claim 50 step (iv), i.e., Wang recites a genus which anticipates the species of Murakawa (Paper 45, p. 11). According to Murakawa, since the use of probes and the detection of hybridized probes, e.g., Southern blot hybridization, were in the public's possession as shown by Mullis (Ex 1013), Wang '727 claim 1 contains all of the

limitations of proposed claim 50 (id.). Murakawa relies on In re Donahue, 766 F.2d 531, 534, 226 USPQ 619, 621-22 (Fed. Cir. 1985) and Brown v. 3M, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001), cert. denied, 122 S. Ct. 1436 (2002) to support its argument.

Here, we agree that Southern blot analysis is such an old and well-known means for detecting DNA of different sizes in a sample that one of ordinary skill in the art would have immediately envisaged using Southern blot analysis to measure PCR amplification products of different sizes regardless of the size of the genus of methods for measuring PCR amplification products generically recited in Wang '727 claim 1. In re Petering, 301 F.2d 676, 682, 133 USPQ 275, 280 (CCPA 1962). Indeed, the Wang '727 specification itself exemplifies determining the amount of amplified product by electrophoresis and visualization of the amplified product by hybridization with a labeled probe, e.g., by extrapolation from an autoradiograph (Ex 2002, c. 11, l. 66 - c. 12, l. 4).

Technically, Murakawa's reply fails to comply with STANDING ORDER § 26(c)(3)², i.e., Murakawa has not provided a specific citation³ by column and line to

² STANDING ORDER § 26(c)(3) reads: "In presenting a reply, a party shall set out in the following order: ... (3) Any additional facts upon which the moving party intends to rely to rebut additional facts alleged by the opposing party with a citation to the evidence and an explanation as to why each additional fact was not set out in the motion."

³ As discussed in STANDING ORDER § 26(a), "Citation to the evidence must be specific, i.e., (1) by column and line of a patent, (2) page, column and paragraph of a journal article and (3) page and line of a cross-examination deposition transcript. Citations to an entire document or numerous pages of a cross-examination deposition transcript do not comply with the requirement for a citation to the record. In this respect, the Trial Section adopts as its policy the rationale of Clintec Nutrition Co. v. Baxa Corp., 44 USPQ2d 1719, 1723 n.16 (N.D. Ill. 1997), which notes that where a party points the court to multi-page exhibits without citing a specific portion or page, the court will not pour over the documents to extract the relevant information, citing United States v. Dunkel, 927 F.2d 955, 956 (7th Cir. 1991). Nor will the board take on the role of an advocate for one of the parties. Compare Ernst Haas Studio, Inc. v. Palm Press, Inc., 164 F.3d 110, 111-12, 49 USPQ2d 1377, 1378-79 (2d Cir. 1999)."

where Mullis (Ex 1013) describes measuring amounts of amplified target and reference sequences by Southern blot hybridization. Mullis (Ex 1013) comprises twenty-six (26) claims, twelve (12) figures and forty (40) columns of disclosure. It is not the function of the Board to search through a record to find evidence supporting a party's position. However, detection of size-distinguishable DNA in a sample using Southern blot analysis was so well known that we decline to dismiss Murakawa's reply for purely technical reasons. However, Murakawa is cautioned to follow the procedural rules set forth in the STANDING ORDER or bear the consequences of failing to do so in the future.

Although Murakawa has argued this as "anticipation," it has also pointed to a difference which makes obviousness the more applicable standard. Wang urges that hold this mislabeling to be dispositive. On the facts of this case we decline to do so. Wang had notice of the substance of Murakawa's argument and thus is not prejudiced. In the final analysis, the question is whether we, on the Director's behalf, are of the opinion that the claims interfere. Whether the analysis is called anticipation or obviousness, we see no patentable distinction on this point.

Based on the above, we find that step (iv) of proposed Murakawa claim 50 is anticipated by Wang '727 claim 1.

3. **Wang '727 claim 1 is not anticipated by proposed Murakawa claim 50 because proposed claim 50 (a) does not explicitly or inherently require use of a shared primer pair to amplify both target and reference sequences as required by Wang claim 1 or (b) recite a sufficiently small genus such that one of ordinary skill in the art would immediately envisage use of a shared primer pair to amplify both target and reference sequences as required by Wang claim 1**

Murakawa argues that

[p]roposed claim 50 has all the elements of claim 1 of the Wang '727 patent except that proposed claim 50 specifies a genus of the reference sequence whereas claim 1 of the Wang '727 patent specifies only a species of the reference sequence, namely, a reference sequence which uses the same primer pair as the target nucleic acid. The genus of proposed claim 50 encompasses the species of claim 1 of the Wang '727 patent. ... The genus of proposed claim 50 includes four species, namely, (i) a synthetic RNA species which does not include the target sequence ..., (ii) a synthetic reference sequence which includes substantially more nucleotides than the target sequence ... and (iii) a sequence including said target and constructed by a multi-base insertion into a site in said viral RNA with respect to said target sequence (Fact 24), which also includes (iv) a sequence which uses the same primer pair as the target sequence for amplification The reference sequence of proposed claim 50 is a small genus which, therefore, anticipates the reference sequence species of claim 1 of the Wang '727 patent. In re Petering, 301 F.2d at 682; Bristol-Myers, 246 F.3d at 1380; In re Schaumann, 572 F.2d at 316-317. As described above, proposed claim 50 also contains the elements of (i) the simultaneous amplification of a sample and predetermined quantity of the reference sequence and (ii) determining the quantity of target nucleic acid present in the sample by comparing the amounts of amplified target nucleic acid and the amount of amplified predetermined quantity of reference sequence. Thus, proposed claim 50 contains all of the elements of claim 1 of the Wang '727 patent, and thereby anticipates claim 1 of the Wang '727 patent, assuming that proposed claim 50 is prior art. PPG Indus., 75 F.3d at 1565. [Paper 38, ¶ bridging pp. 19-20, citations to Murakawa's "STATEMENT OF MATERIAL FACTS SUPPORTING THE MOTION" omitted.]

Furthermore, according to Murakawa, "[p]roposed claim 50 is claim 27 as originally filed in Murakawa's involved application written in independent form incorporating all of the limitations of the claims from which it depends, i.e., claims 26 and 18" (id., p. 1).

In rebuttal, Wang presents three arguments. First, Wang contends that "the Board has already ruled that [original] claim 27 [i.e., proposed claim 50] does not contain every limitation of, and thus cannot anticipate, Wang claim 1" (Paper 44, p. 19).

In the Decision on Wang Preliminary Motion 1 (Paper No. 36), at p. 22, the Board held that "none of the earlier Murakawa claims, i.e., Murakawa claims filed or pending as of June 15, 1994 ... are directed to the same or substantially the same invention as claimed in the Wang 1993 patent because ... none require or necessarily result in use of shared primer pairs." The "earlier Murakawa claims" include Murakawa claim 27. Paper No. 36 at 13, n.11. The "invention claimed in the Wang 1993 patent" includes the invention of Wang claim 1. Thus, the Board has already ruled that claim 27 differs in a material limitation from Wang claim 1. However, anticipation requires that every limitation of a claim can be found, either expressly or inherently, in a prior art reference. See e.g., Verdegaal Bros., 814 F.2d at 631, 2 USPQ2d at 1053. Consequently, the Board has already ruled that claim 27 does not contain every limitation of, and thus cannot anticipate, Wang claim 1. [Paper 44, ¶ bridging pp. 18-19.]

Therefore, Wang contends, again citing to the Decision on Wang Preliminary Motion 1 (Paper 36, p. 22, "binding to a shared primer pair is neither excluded, required nor a necessary result"), that Murakawa should not be allowed to construct a genus that explicitly recites shared primer pairs (Paper 44, ¶ bridging pp. 19-20). In reply, Murakawa argues that its "[p]roposed claim 50 encompasses a genus of reference sequences, including the species of a reference sequence that uses a shared primer pair with the target, as recognized by the Board" (Paper 45, p. 12).

The question joined by Wang and Murakawa is whether one skilled in the art, given the genus of reference sequences recited in proposed Murakawa claim 50, would "at once envisage" the species of Wang '727 claim 1, i.e., a reference sequence which binds to the same primers as are bound by the target sequence in a PCR amplification reaction. Petering, 301 F.2d at 682, 133 USPQ at 280.

Wang's second argument answers the above question in the negative. Wang points out that the process of proposed Murakawa claim 50 uses "at least one synthetic

RNA sequence which does not include said target sequence or which includes substantially more nucleotides than said target sequence" (Paper 44, p. 20).⁴

According to Wang, the recited synthetic RNA sequence "can be any synthetic RNA sequence, of any size, limited only in that it does not include the target sequence" or a "'synthetic RNA sequence ... which includes substantially more nucleotides than said target sequence' ... which is limited, not by sequence, but by size" (*id.*). In either case, Wang argues that the number of possible sequences encompassed thereby constitutes an infinitely large genus (*id.*). Wang further argues that the deposition testimony of Dr. Joyce (Ex 2030 at pp. 23:16-27:25), Murakawa's expert witness, "clearly suggests that there are uncalculated species within the genus of claim 18 (and so within the genus of proposed claim 50)" (*id.*).

22. Dr. Gerald F. Joyce testified (Ex 2030 at pp. 23:16-27:25)

Q. Let's look at Paragraph 13. In this paragraph you point to this specific passage that you quote from Claim 18 about, synthetic RNA sequence which does not include the target sequence or which includes substantially more nucleotides than said target sequence.

A. Yes.

Q. Now, that phrase includes numerous possibilities, doesn't it?

A. Yes, it does.

Q. One possibility is that you have a reference sequence that's the same length as the target sequence but does not include the target sequence, right?

A. That's a possibility.

Q. And for that possibility you cannot use shared primer pairs, right?

⁴ The Decision on Wang Preliminary Motion 1 noted that

(i) the testimony of two expert witnesses, i.e., Drs. Joyce and Ehrlich, agreed that the term "substantially more", in the context of Murakawa '450 claims 18, 19 and 30, did not have an ordinary and customary meaning to one skilled in the art (Paper 36, p. 17) and

(ii) a control sequence that contains "substantially more" nucleotides than a target sequence, but does not contain any of the target sequence, could not use a shared primer pair (*id.*, p. 18).

A. For that possibility you could not use shared primer pairs, correct.

Q. Isn't it also true that you'd need to use at least two probes to detect and distinguish the target from the reference under that possibility?

A. Not necessarily. It would be possible to place a target sequence for the probe within the reference sequence and have no other aspect of the reference sequence be the target sequence. In other words, you could have an exogenous probe sequence in both a target and a reference that isn't part of the natural target sequence. I'm just, it just is a possibility.

Q. Okay. So you could have an insert into a reference sequence that contained none of the target sequence?

A. Correct.

Q. And then have that insert be the target for the probe?

A. That could be done.

Q. Okay. A second possibility is that you could have a reference sequence that contains substantially more nucleotides than the target sequence but does not contain the target sequence, right?

A. Yes, that's another possibility.

Q. And with this second possibility with the exception that you gave before you'd need at least two probes to test for false negatives, right?

A. All right, let's get the facts here straight. Put the whole thing together again. I want to answer correctly here.

Q. Sure. That's fine. Now, a second possibility we're talking about where the reference sequence contains substantially more nucleotides than the target sequence.

A. Right.

Q. For that you would need to have two probes to test for false negatives unless you made the insertion for the probe that you talked about early?

A. You said it slightly different the second time. I don't want to put words in your mouth. But I think what you mean is for that circumstance where the reference contains substantially more nucleotides than the target sequence and doesn't contain any of the target sequence.

Q. That's right.

A. And excluding the possibility of inserting a probe hybridization sequence within both the target and reference sequence would you then require separate primer pairs; is that the question?

Q. Yes.

A. And the answer is, yes, that's possible.

Q. And it's also true for this second possibility that you cannot use shared primers, right?

A. It's possible for this second possibility contingent on

excluding the insertion of the probe sequence that you could not use shared primers. You can see why I had trouble with this, too. There's many possibilities allowed within this claim.

Q. Let me, let's talk about a third possibility. A third possibility is you have a reference sequence like the second one we talked about, except that it contains substantially fewer nucleotides than the target sequence, right?

A. That is a possible construction.

Q. And for that possibility you cannot use shared primers, right?

A. If there's, again, with the restriction there's no exogenous insertion of hybridization sites beyond the starting sequences. So with that caveat on top of that possibility, yes, that's another way in which you could in principle operate without shared primer pairs.

Q. And the answer you gave about needing two probes for the first and second possibilities, the same answer would apply to the third possibility?

A. It could apply to the third possibility as well.

Q. Now, I'm going to talk about something that you mentioned before which is I think there are fourth, fifth, and sixth possibilities.

A. At least.

Q. Which are the same as the first three except the reference sequence contains part of the target sequence, right?

A. Yes.

Q. And all of those fourth, fifth, and sixth possibilities can be practiced without the use of shared primer pairs, right?

A. Optionally they could be practiced without the use of shared primer pairs, yes. Not necessarily, but optionally.

Q. If the portion of the target sequence used in the reference sequence did not include the portion to which one of the primers of the target sequence binds, then it would not be used, possible to use shared primer pairs, right?

A. Excluding the possibility of exogenous placement of hybridization sites for primers and/or probes, yes.

In reply, Murakawa focuses its response on the second of the two Markush members recited in its proposed claim 50, i.e., a synthetic RNA sequence which includes substantially more nucleotides than the target sequence (Paper 45, pp. 12-13). Murakawa argues that "the only difference between the size differentiating reference sequence claim 1 of the Wang '727 patent [see step (b), "wherein said amplified target

and standard segments are distinguishable by size"] and the reference sequence of proposed claim 50 which differs from target sequence by containing substantially more nucleotides is that claim 1 of the Wang '727 patent uses a shared primer pair with the target sequence" (Paper 45, p. 13).

Use of a shared primer pair is precisely the limitation at issue. It is not a matter of size so much as sequence. Use of a shared primer pair requires that the target and reference sequences share a common nucleotide sequence (see e.g., Paper 36, p. 2, n.1, primers are designed to be complementary to the bases at the 3' ends of a target DNA sequence).

Assuming arguendo that reference sequences distinguishable by size from target sequences constitute a defined, albeit very large, genus, the question is still whether one skilled in the art would "at once envisage" reference sequences having 3' end nucleotide sequences in common with a target sequence, i.e., reference sequences which bind to the same primers as the target sequence in the same PCR amplification reaction mixture.

In view of this record, including the testimony of Dr. Joyce cited above, we find that proposed Murakawa claim 50 would not have immediately suggested using a reference sequence which binds to the same primers as the target sequence in the same PCR amplification reaction mixture. The definition of a reference sequence distinguishable from a target sequence by size is broad and general and does not particularly suggest a reference sequence which binds to the same primer pair as a target sequence. For example, the Murakawa '450 specification suggests using a

reference sequence which is "present in the expression products of all or virtually all of the cells of a ... sample" (Ex 2006, p. 4). An "ubiquitous" reference sequence may be size-distinguishable and sequence-distinguishable from a target sequence, which may or may not be present in a sample. Thus, regardless of whether a size-distinguishable class of reference sequences encompasses a vast, perhaps infinite number of reference sequences, Murakawa has not pointed us to an explicit or implicit suggestion of a more limited class of reference sequences which binds to the same primers as the target sequence in the same PCR amplification reaction mixture as recited in Wang '727 claim 1.

While Dr. Joyce has testified to the possibility of this limited class within the broad class of size-distinguishable reference sequences, the issue is whether proposed Murakawa claim 50 identifies reference sequences that bind to the same primer pairs as are bound to a target sequence in a PCR reaction with sufficient specificity to constitute a description thereof within the purview of 35 U.S.C. § 102. On this record, we think not. As noted by Wang in its opposition (Paper 44, ¶ bridging pp. 20-21), the rationale of Petering, Schaumann and Bristol-Myers is not applicable to the facts of this case. The "prior art genus" of proposed claim 50 does not consist of a few species with a common structure such that one of ordinary skill in the art would "at once envisage each member" of the encompassed species.

Finally, Wang argues that

it should be noted that the reference sequence of Murakawa proposed claim 50 is limited to viral RNA, while claim 1 of the Wang '727 patent recites "nucleic acids." In this aspect, the Wang claim is broader than Murakawa proposed claim 50. Claim 8 of the Wang '727 patent, which

depends indirectly from claim 1, explicitly relates to quantitation of HIV proteins, among others. However, Murakawa does not argue that its claims are directed to the same patentable invention as claim 8 of the Wang '727 patent, and pursuant to Section 13.7 of the Standing Order, Murakawa should not be heard to do so in its reply. [Paper 44, p. 21.]

Except for Murakawa's general response noted above, i.e., the only difference between the reference sequences of Wang '727 claim 1 and proposed Murakawa claim 50 is that the reference sequence of Wang '727 claim 1 uses a shared primer pair with the target sequence, no more specific response to Wang's final argument is apparent in Murakawa's reply (Paper 45, pp. 12-13).

Based on the above, we find that Wang '727 claim 1 is not anticipated by proposed Murakawa claim 50, assuming proposed claim 50 to be prior art with respect to Wang '727 claim 1.

4. combining proposed Murakawa claim 50 with the 1988 Murakawa article (Ex 1012) and the Cantin '802 patent (Ex 1020) does not lead to the invention of Wang '727 claim 1.

First, as noted by Murakawa in its reply (Paper 45, p. 14), obviousness is determined "at the time the invention was made." 35 U.S.C. § 103(a). Assuming arguendo that Wang '727 claim 1 is entitled to its earliest possible effective filing date of August 21, 1989, then both the 1988 Murakawa article (Ex 1012)^[5] and the Cantin '802 patent^[6] qualify as prior art against Wang '727 claim 1.

Second, as moving party, Murakawa has the burden of establishing by a

⁵ Murakawa et al., "LABORATORY METHODS: Direct Detection of HIV-1 RNA from AIDS and ARC Patient Samples," DNA, Vol. 7, No. 4, pp. 287-295 (1988) (Ex 1012, "the 1988 Murakawa article").

⁶ U.S. Patent 5,110,802 issued May 5, 1992 to Cantin et al. (Cantin), entitled "Oligonucleotide Phosphonates and Method of Inhibiting a Human Immunodeficiency Virus in vitro Utilizing Said Oligonucleotide Phosphonates" (Ex 1020). Cantin is based on application 07/073,189, filed July 14, 1987.

preponderance of the evidence, that the invention of Wang '727 claim 1 would have been obvious over proposed Murakawa claim 50 in view of the 1988 Murakawa article and the Cantin '802 patent.

According to Murakawa, its proposed claim 50 differs in failing to recite a reference sequence which is PCR amplified simultaneously with the target sequence using the same primer pair as required by Wang '727 claim 1. Further according to Murakawa, the 1988 Murakawa article discloses (i) a reference sequence that is a target sequence with a multi-base insertion and (ii) use of a shared primer pair to amplify target and reference sequences simultaneously **for confirmation of negative results** (Paper 38, pp. 10-11, asserted facts 29 and 30). Murakawa directs our attention to Ex 1012, "page 292, right column above Fig. 7, Fig. 7 legend and Fig. 8 legend" and "page 293, first full paragraph" (id.). Still further according to Murakawa,

[iii] [t]he Cantin '802 patent discloses the simultaneous PCR amplification of a target viral RNA sequence and a fixed concentration of a reference sequence with an insert between the primer sites of the target sequence. MX 1020 at column 4, lines 45-53. [and]

[iv] ... that the initial amount of reference sequence template remains constant thereby enabling one **to determine the ratio of amplification of the reference sequence template versus the sample template before and after treatment to determine the effect of treatment on viral RNA synthesis.** MX 1020 at column 4, lines 57-60 and lines 44-45. [Paper 38, p. 14, asserted facts 48 and 49, emphasis added.]

Thus, Murakawa contends that "[i]t would have been obvious to use the reference sequence of Murakawa et al. (MX 1012) in the process for the quantitation of a target viral RNA sequence of proposed claim 50 in light of the Cantin '802 patent (MX 1020) with a reasonable likelihood of success" (Paper 38, ¶ bridging pp. 20-21).

Assuming arguendo that it would have been obvious to use the reference sequence of the 1988 Murakawa article (Ex 1012) as the synthetic RNA reference sequence in the method of proposed Murakawa claim 50 in light of the Cantin' 802 patent (Ex 1020), such a combination would not lead to the invention of Wang '727 claim 1.

First, although the preamble of proposed claim 50 recites a "process for quantitation of a target viral RNA sequence, "proposed claim 50 does *not* contain the step of calculating the [absolute] amount of target RNA in the sample that is found in claim 1 of the Wang '727 patent" (Wang's opposition, Paper 44, p. 22). Instead, proposed claim 50 recites "determining the **relative quantification** of the target sequence" (step (v), emphasis added).

Second, the 1988 Murakawa article discusses direct detection of HIV-1 nucleic acid sequences (i.e., without a prior culturing step) by a two-step technique -- viral RNA is transcribed back into its complementary DNA followed by PCR amplification of the transcribed DNA (i.e., a reverse-transcription PCR). According to the 1988 Murakawa article, a prokaryotic T7 RNA polymerase promoter sequence was appended to one of the priming oligonucleotides (i.e., HTLVAT7) to enhance the efficiency of the PCR technique (Ex 1012, abstract). HTLVAT7 adds 22 bases constituting the promoter recognition sequence for T7 RNA polymerase to primer HTLVA (id., p. 288, c. 2, second sentence, last paragraph). Figure 7 of the 1988 Murakawa article illustrates PCR amplification of known amounts of RNA, i.e., 0.1 ng prepared from target pGM92 (containing the 3' open reading frame of HIV) and reference pGM92+21 sequences,

obtained using an HTLVAT7 oligonucleotide in place of the HTLVA oligonucleotide primer and suggests "a significant amplification by the transcription step" using T7 RNA polymerase (Ex 1012, p. 292, Fig. 7 legend, and paragraph bridging pp. 292-293).

Assuming arguendo that pGM92+21 is a reference sequence according to proposed claim 50 (i.e., a synthetic RNA sequence which includes substantially more nucleotides than said target sequence), the 1988 Murakawa article discusses making such

an internal control within our PCR reactions by constructing a plasmid with a small insertion in the targeted region **to determine whether the PCR reaction is successful**. Thus, negative results for HIV-1 detection from our clinical samples are most likely the result of the absence of virus. [Ex 1012, p. 293, first full paragraph, emphasis added.]

Murakawa does not point out, and we do not find, where the 1988 Murakawa article describes or suggests using the described internal control as a means for quantitating the actual amount of a target viral nucleic acid sequence in a sample. Rather, the 1988 Murakawa article suggests using HTLVAT7 "to direct specific and efficient T7 RNA polymerase-mediated transcription of that amplified sequences, thus enhancing the sensitivity and simplifying the labor of the experiment" (Ex 1012, abstract). Moreover, Murakawa's reply does not dispute Wang's statement that "the only example in the Murakawa publication in which quantitation is performed does not employ shared primers (see Exhibit 1012, Fig. 4, p. 291)" (Paper 44, p. 22).

Third, according to its abstract, the Cantin '802 patent (Ex 1020) is directed to "[a] method of inhibiting human immunodeficiency virus (HIV) comprising administering a therapeutically effective amount of an antiviral agent to attack the first splice acceptor site of the tat III gene of HIV." Murakawa cites to the following text in the Cantin '802

patent (complete paragraph presented).

A modified polymerase chain reaction amplification assay was also used in accordance with the present invention to determine the effect of the OMP [i.e., oligodeoxyribonucleoside methylphosphonates⁷] treatment on viral RNA synthesis. Details of this amplification procedure are disclosed in copending application Ser. No. 941,379,^[8] filed Dec. 15, 1986 with the exception that a modified version of the HIV 3' ORF region is constructed such that the sequences between the two primer sites are altered in length and composition. Such a modification allows for a control RNA or DNA template of fixed concentration to be made which is included with the experimental RNA or DNA samples. The probe for identifying this altered sequence is different from that used for the HIV samples, thereby enabling differentiation of the template amplification from the HIV sequence amplification. The amount of the altered template remains constant thereby enabling one to determine the ratio of amplification of the altered template versus the authentic HIV templates. [Ex 1020, c. 4, ll. 42-60.]

It is clear that the Cantin '802 patent allows one of ordinary skill in the art to determine whether treatment with an antiviral agent, i.e., OMP, has an affect on viral growth. However, as pointed out by Wang (Paper 44, p. 11, fact 68), "[t]he Cantin '802 patent (Exhibit 1020) does not contain the step of calculating the amount of target RNA in the sample that is found in claim 1 of the Wang '727 patent." Murakawa admits as much argues that "the Cantin '802 patent suggests the calculation of the amount of the target sequence through a comparison with the known amount of reference sequence" (Paper 45, p. 3, ¶ 1). Suggesting a comparison, e.g., making a relative, semi-

⁷ Cantin explains antisense RNA as a naturally occurring regulatory control sequence that directs synthesis of RNA and is complementary to a specific mRNA (Ex 1020, c. 1, ll. 18-26). The OMPs of Cantin are analogs in which a 3'-5' methylphosphonate linkage replaces the phosphodiester linkage found in naturally occurring nucleic acids (*id.*, c. 1, ll. 59-63). Thus, the OMPs maintain the complementarity, i.e., specificity, of an antisense RNA but can be used to inhibit mRNA translation thereby reducing viral DNA and infectious virus production (*id.*, c. 1, l. 64 - c. 2, l. 15; c. 2, ll. 35-67).

⁸ According to PTO records, application 06/941,379 is now abandoned.

quantitative estimation, is not the same thing as calculating the actual amount.

The cited portion of the Cantin '802 patent simply discusses altering the length and composition of "the sequences between the two primer sites." Murakawa has presented no evidence that one of ordinary skill in the art would have understood this to have meant using the same primer pair to amplify simultaneously target and reference sequences in the same PCR reaction. Moreover, according to the Cantin '802 patent the details of the amplification procedure are disclosed in an abandoned application, i.e., application 06/941,370. The Cantin '802 patent does not provide (nor has Murakawa) the details which Murakawa argues "suggest" the invention of Wang '727 claim 1. Instead, Figure 2 of the Cantin '802 patent suggests visually comparing relative signal ratios between various samples. According to the Cantin '802 patent,

[t]he lanes shown in FIG. 2 are as follows: A, in vitro transcript of amplified region with 10^{-7} μ M concentration of a non-specific OMP complementary to HSV I (herpes simplex virus I) sequences; C and D, positive controls from cells infected with HIV in the absence of OMP treatment; E, sample from HIV infected cells pretreated with OMP-C, the sense sequence; F, sample from HIV infected cells pretreated with OMP-A, the antisense sequence. For each reaction involving HIV infected cells, 1 μ gm of total cellular RNA was used for amplification. After the amplified DNA were subjected to gel electrophoresis, blotted to a nylon filter membrane, and hybridized to detection probes, the filter was exposed to x-ray film for 12 hours to obtain the exposure of FIG. 2. [c. 5, ll. 7-25.]

Based upon the foregoing, proposed Murakawa claim 50, the 1988 Murakawa article and the Cantin '802 patent all appear to relate to determining "relative" amounts of RNA. In other words, reading both the 1988 Murakawa article and the Cantin '802 patent as being directed to detecting the presence or absence of a target RNA sequence relative to a predefined amount of a control or reference nucleic acid

sequence is entirely consistent with "determining the relative quantification of the target sequence" as recited in proposed claim 50, e.g., whether the target sequence is present or absent in the sample. Moreover, insofar as Murakawa argues that its proposed claim 50 is claim 27 as originally filed (Paper 38, p. 1), we note that original claim 27 ultimately depended on original independent claim 18 which recited "a process for minimizing false negative data in the identification of a target viral RNA sequence in a peripheral blood cell sample" (Ex 1015, p. 3). Thus, original claim 27 also suggests that proposed claim 50 is directed to detecting a target RNA sequence in a method having a minimum level of sensitivity based on the ability to detect an amplified product of a known amount of a reference sequence.

Combining proposed Murakawa claim 50 with the 1988 Murakawa article (Ex 1012) and the Cantin '802 patent (Ex 1020) as suggested by Murakawa does not lead to the invention of Wang '727 claim 1. None of proposed Murakawa claim 50, the 1988 Murakawa article or the Cantin '802 patent, alone or in combination, disclose or suggest determining the actual amount of target sequence by simultaneously amplifying the target nucleic acid sequence and a known amount of an added reference sequence with the same primer pair in a single reaction mixture as recited in Wang '727 claim 1. Obviousness requires a suggestion of all limitations in a claim. In re Royka, 490 F.2d 981, 985, 180 USPQ 580, 583 (CCPA 1974).

B. Conclusion

Based on the foregoing, the invention of Wang '727 claim 1 is not the same patentable invention as the invention of proposed Murakawa claim 50 because Wang

'727 claim 1 is neither anticipated by proposed Murakawa claim 50 nor rendered obvious by proposed Murakawa claim 50 in view of the 1988 Murakawa article and the Cantin '802 patent. Specifically, Wang '727 claim 1 is not anticipated by proposed Murakawa claim 50 because proposed claim 50 (a) fails to require, explicitly or inherently, use of a shared primer pair to amplify both target and reference sequences as required by Wang claim 1 and (b) fails to recite a sufficiently small genus of reference sequences that one of ordinary skill in the art would immediately envisage use of shared primer part to amplify both target and reference sequences as required by Wang claim 1. Alternatively, Wang '727 claim 1 is not rendered obvious by the "prior art" because, assuming arguendo that one of ordinary skill in the art would have been motivated to combine proposed Murakawa claim 50, the 1988 Murakawa article and the Cantin '802 patent with a reasonable expectation of success, this "prior art" would have not have suggested calculating the actual amount of target nucleic acid in a sample as required by Wang claim 1. Since Wang '727 claim 1 and proposed Murakawa claim 50 do not define the same patentable subject matter, there is no interference-in-fact between the subject matter of any of the claims of the 1993 and 1995 Wang patents and the subject matter of proposed Murakawa claim 50. Consequently, we need not, and do not reach, whether proposed Murakawa claim 50 is unpatentable under 35 U.S.C. §§ 112, 102, 103 and/or 135(b).

ORDERED that Murakawa preliminary motion 1 is **denied**.

Carol A. Spiegel
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Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

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